UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,367	05/11/2001	Francis Michon	3842-4050	5710

7590 06/24/2004

MORGAN & FINNEGAN, L.L.P.
345 Park Avenue
New York, NY 10154-0053

EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,367	MICHON ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on th cover she t with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-33* is/are pending in the application.

4a) Of the above claim(s) *12,19-28 and 30-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-11,13-18 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *81103*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 03/22/04 has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' after-final amendment filed 12/22/03 in response to the final Office Action mailed 06/20/03.

Status of Claims

3) Claims 1, 11, 13, 17 and 29 have been amended via the amendment filed 12/22/03. It is noted that claim 12 has also been amended to change claim dependency, yet is not indicated as being '(currently amended)'.

Claims 1 and 4-33 are pending.

Claim 12, now dependent from claim 31, has been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 1, 4-11, 13-18 and 29 are under examination.

Information Disclosure Statement

4) Acknowledgment is made Applicants' Information Disclosure Statement filed 08/11/03. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Prior Citation of Title 35 Sections

5) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

6) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Moot

7) The rejection of claim 12 made in paragraph 26 of the Office Action mailed 06/20/03 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is moot in light of Applicants' amendment to the claim changing its dependency to a non-elected claim.

8) The rejection of claim 12 made in paragraph 27(b) of the Office Action mailed 06/20/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' amendment to the claim changing its dependency to a non-elected claim.

Rejection(s) Maintained

9) The rejection of claims 1, 4-11, 13-18 and 29 made in paragraph 26 of the Office Action mailed 06/20/03 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is maintained for reasons set forth therein and herebelow.

Applicants state that page 6 at lines 13-23 of the instant specification describes a hyaluronic acid useful for eliciting an immune response, where the epitope that is cross-reactive with group A and group C streptococci is located at the non-reducing terminal glucuronic acid or unsaturated glucuronic acid of the hyaluronic acid. Applicants further submit that one skilled in the art would understand that hyaluronic acid moieties refer to a 'part, portion or share' of the hyaluronic acid or the 'poly-glucaronic acid portion'.

Applicants' arguments have been carefully considered, but are non-persuasive. The specification at lines 13-33 of page 26 are reproduced herebelow:

> response. In particular, HA is useful for raising an immune response that is cross-reactive with bacteria, such as group A and group C streptococci, that have HA on their surface. Without being bound by any theory, it is believed that the epitope cross-reactive with group A and group C streptococci is about 3 or 4 residues in length and is located at the nonreducing terminal. There does not appear to be a significant difference whether the non-reducing terminal glucuronic acid residue is saturated or unsaturated as both epitopes are protective. In addition, it appears that the terminal glucuronic acid is converted to unsatirated glucuronic acid in blood and other body fluids. HA can terminate in either a glucosaminyl or glucuronyl residue, the immune response is enhanced when the percentage of glucuronic acid or unsaturated glucuronic at the nonreducing terminal of HA is increased over the percentage of N-acetylglucosamine.

This portion of the specification does not provide descriptive support for hyaluronic acid 'moeities', or for covalently bound or conjugated low molecular weight hyaluronic acid with a molecular weight of from about 600 daltons to about 400 kilodaltons wherein the conjugate 'induces an immune response to epitopes comprising the non-reducing terminal glucuronic acid or

unsaturated glucuronic acid residues of said hyaluronic acid moeities'. While there is support within the instant specification for limitations, such as, 'LMW-HA molecules' or 'LMW-HA fragments', there is no descriptive support for LMW-HA 'moieties'. Furthermore, no where in the specification the limitation 'moieties' is equated to 'part, portion or share' of the hyaluronic acid or the poly-glucaronic acid portion. The rejection stands.

Rejection(s) Withdrawn

10) The rejection of claim 13 made in paragraph 27(a) of the Office Action mailed 06/20/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

11) The rejection of claims 17, 18 and 29 made in paragraph 27(b) of the Office Action mailed 06/20/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

12) The rejection of claims 1, 4-10 and 13-16 made in paragraph 28 of the Office Action mailed 06/20 under 35 U.S.C. § 103(a) as being unpatentable over Fillit *et al.* (*J. Exp. Med.* 168: 971-982, 1988) in view of Kazuo *et al.* (JP 9012600), Nebinger *et al.* (*J. Chromatol.* 265: 19-25, 1983, already of record) (Nebinger *et al.*, 1983), or Nebinger *et al.* (*J. Chromatol.* 320: 351-359, 1985, already of record) (Nebinger *et al.*, 1985), or Shimada *et al.* [*J. Biochem* (*Tokyo*) 96: 721-725, 1984, already of record], or Ulrich *et al.* (*Hoppe-Seyler's Z. Physiol. Chem.* 360: 1457-1463, 1979, abstract - already of record) and Kazuo *et al.* (JP 9012600) and Fillit *et al.* (*J. Exp. Med.* 164: 762-776, 1986, already of record) (Fillit *et al.*, 1986), is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

13) The rejection of claim 11 made in paragraph 29 of the Office Action mailed 06/20 under 35 U.S.C. § 103(a) as being unpatentable over Fillit *et al.* (*J. Exp. Med.* 168: 971-982, 1988) as modified by Kazuo *et al.* (JP 9012600), Nebinger *et al.* (*J. Chromatol.* 265: 19-25, 1983, already of record) (Nebinger *et al.*, 1983), or Nebinger *et al.* (*J. Chromatol.* 320: 351-359, 1985, already of record) (Nebinger *et al.*, 1985), or Shimada *et al.* [*J. Biochem* (*Tokyo*) 96: 721-725, 1984, already of record], or Ulrich *et al.* (*Hoppe-Seyler's Z. Physiol. Chem.* 360: 1457-1463, 1979, abstract - already of record) and Kazuo *et al.* (JP 9012600) and Fillit *et al.* (*J. Exp. Med.* 164: 762-776, 1986, already of record) (Fillit *et al.*, 1986) as applied to claim 1 above, and further in

view of Blake *et al.* (US 5,439,808, already of record) and Philip *et al.* (US 6,054,127, already of record), is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

Rejection(s) under 35 U.S.C § 112, First Paragraph

14) Claims 1, 4-11, 13-18 and 29 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The base claim 1 and claim 13, as amended, include the new limitations: 'physiologically suitable polypeptide carrier' and 'bacterial or viral polypeptide'. Applicants point to lines 10-22 on page 11 of the specification as providing descriptive support for these limitations. However, lines 10-22 on page 11 of the specification describe a 'physiologically tolerated protein or polypeptide' and polypeptide carriers of narrower scope, such as, immunogenic polypeptides from specific bacteria: streptococci, pneumococci, *Haemophilus*, *Neisseria* and *E. coli*, as opposed to generic 'bacterial polypeptide' of broader scope. Similarly, while this part of the specification describes one species of 'an immunogenic polypeptide from influenza', does not describe the broader 'viral polypeptide' genus. Therefore, the added limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or invited to point to specific pages and line numbers in the specification where support for such recitations can be found.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

15) Claims 1, 4-11, 13-18 and 29 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 lacks proper antecedent basis in the limitation 'unsaturated glucuronic acid residues' (see line 9). Since the limitation is already recited in the earlier part of the claim, for

proper antecedence, it is suggested that Applicants replace the limitation with --the unsaturated glucuronic acid residues--.

(b) Claim 16 has improper antecedent basis in the limitation: 'the bacterium is'. Claim 16 depends from claim 15, which does not recite a 'bacterium'.

(c) Claim 16 is further confusing and/or incorrect in the limitation: 'the bacterium is ..... streptococci'. 'Streptococci' are 'bacteria' and 'streptococcus' is a 'bacterium'.

(d) For proper antecedence and to be consistent with the claim language used in rest of the examined claims. including claim 29, in claim 17, it is suggested that Applicants replace the limitation 'the conjugate according to claim 1' with --the immunogenic conjugate according to claim 1--.

(e) Claims 4-11, 13-18 and 29 which depend, directly or indirectly, from claim 1, are also rejected as being indefinite because of the vagueness or indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C § 102

16) Claims 1, 4-10, 13, 17 and 18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Simon *et al.* (WO 00/12122, published 03/09/00 - original and English translation are already of record) as evidenced by Werries *et al.* (*Mol. Biochem. Parasitol.* 7: 127-140, 1983) and Nebinger *et al.* (*J. Chromatol.* 320: 351-359, 1985, already of record) (1985).

The page numbers indicated below refer to the page numbers in the translated document. The term 'immunologically-suitable' is interpreted as antigenically suitable.

Simon *et al.* disclosed low molecular weight hyaluronic acid (HA) fragments covalently coupled to an antigen (i.e., inclusive of an antigenically- or immunologically-suitable polypeptide), peptide, adjuvant or a carrier, and their advantageous use as immunogenic vaccines for *in vivo* administration (see abstract; pages 3, 5-8 an 12; pages 25, 26 and 29; pages 30, 31, 33 and 36; and claims 25-29 and 31-33). The antigen or peptides used to couple to the low molecular weight HA are those 'that are usually employed in vaccines' (see page 34). The covalent coupling between the two components may be direct and involves reducing with $NaBH_3$ (see Example 8). The HA coupled to the antigen/peptides induces specific T-cell-imparted immune response and is administered locally, systemically or intravenously (see pages 33, 34 and 38). The HA fragments

produced by hydrolysis of high molecular weight hyaluronic acid using streptococcal or bull's testicular hyaluronidase contain 1 to 50 basic units (see pages 12 and 13; Example 3). Simon's HA fragments are of size 14, 16, 21 and 45 (see Tables 1-3 and 5) or fragments containing 2 to 20 basic units. Suitable antigens used are virus antigens; tyrosinase (i.e., an immunologically suitable polypeptide); and GP-33 antigen of LCM virus (see pages 29 and 39; and Table 7). The manner of coupling between the antigen carrier and the glucuronic acid-containing HA is not particularly restricted (see page 34), and therefore encompasses any method of coupling. The vaccine may further comprise customary additives or Freund's adjuvant (see pages 31 and 37), or liposomes and microsomes (see page 39).

That hyaluronic acid fragments of the prior art have a molecular weight of from about 600 daltons to about 400 kilodaltons is inherent from the teachings of Simon *et al.* in light of what is known in the art. For instance, Werries *et al.* teach the molecular weight of hyaluronate oligosaccharides of about hexasaccharide size to be 75,000 (see abstract), and thus indicating that Simon's HA fragments inherently fall the recited molecular weight range. That the prior art vaccine contains greater than 50% to 99% low molecular wight HA possessing a non-reducing terminal glucuronic acid is also inherent from the teachings of Simon *et al.* in light of the fact that the prior art HA were produced by treatment with bull's testicular hyaluronidase. For instance, Nebinger *et al.* (1985) taught that testicular hyaluronidase cleaves hyaluronic acid to give a homologous series of oligosaccharides with glucuronic acid in a terminal non-reducing position (see page 351).

The teachings of Simon *et al.* anticipate the instant claims. Werries *et al.* or Nebinger *et al.* is **not** used as a secondary reference in combination with Simon *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Simon *et al.* with the unrecited limitation(s) being inherent in view of what is known in the art as explained above. See *In re Samour* 197 USPQ 1 (CCPA 1978).

17) Claims 1, 14-16 and 29 are rejected under 35 U.S.C. § 102(b) as being anticipated by Simon *et al.* (WO 00/12122, published 03/09/00 - original and English translation are already of record) as evidenced by Kazuo *et al.* (JP 9012600, original and English translation) and Fillit *et al.* (*J. Exp. Med.* 168: 971-982, 1988, already of record).

The disclosure of Simon *et al.* is explained above. Although Simon *et al.* are silent about the elicitation by their conjugate of antibodies that bind to group A or group C streptococci, or to an epitope comprising glucuronic acid as the nonreducing terminal sugar of a low molecular weight HA moiety, or elicitation of anti-low molecular weight HA antibodies in humans, Simon's low molecular wight HA-viral antigen conjugate is expected by those of skill in the art to elicit such antibodies. That Simon's conjugate elicits such antibodies is inherent from the disclosure of Simon *et al.* in light of what is known in the art. For instance, Kazuo *et al.* have demonstrated that low molecular weight HA covalently coupled to a protein elicits antibodies that bind specifically with hyaluronate in a vertebrate host such as mice (see abstract; claims; sections 0015, 0019, and 0025- 0029 of the translated document). Therefore, Simon's low molecular wight HA-viral antigen conjugate is expected to elicit HA-specific antibodies in another vertebrate host, such as, human host. That the prior art hyaluronidase-depolymerized low molecular weight HA conjugate elicits antibodies that bind to an epitope comprising non-reducing terminal glucuronic acid is also inherent from the teachings of Simon *et al.* in light of what is known in the art. For instance, Fillit *et al.* (1988) taught that testicular hyaluronidase treatment uniquely exposes a specific terminal hyaluronic acid antigenic sites or immunodeterminants comprising glucuronic acid and enhances its antigenicity (see pages 974; 977 and 978), and showed that hyaluronidase-depolymerized low molecular weight, conjugated HA induced antibodies with specificity for terminal glucuronic acid in rabbits (see Results; and page 975).

The teachings of Simon *et al.* anticipate the instant claims. Kazuo *et al.* or Fillit *et al.* (1985) is **not** used as a secondary reference in combination with Simon *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Simon *et al.* with the unrecited limitation(s) being inherent in view of what is known in the art as explained above. See *In re Samour* 197 USPQ 1 (CCPA 1978).

Rejection(s) under 35 U.S.C § 103

18) Claim 11 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Simon *et al.* (WO 00/12122, published 03/09/00 - original and English translation are already of record) as applied to claim 1 above, and further in view of Blake *et al.* (US 6,451,317 B1).

The reference of Blake *et al.* is applied in this rejection because it qualifies as prior art

under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

The teachings of Simon *et al.* are explained above, which do not teach an immunogenic meningococcal protein or polypeptide as a polypeptide carrier in their conjugate.

However, the use of bacterial protein or polypeptide as a protein carrier for conjugating to a polysaccharide to increase its immunogenicity was well known in the art. For instance, Blake *et al.* taught the use of meningococcal porin or outer membrane protein as a carrier in a conjugate to boost the immune response towards a bacterial polysaccharide. More importantly, Blake *et al.* taught the advantageous nature of meningococcal porin or OMP in that it also serves as an adjuvant (see paragraph bridging columns 2 and 3; last two full paragraphs in column 2; and first full paragraph in column 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to covalently couple Blake's meningococcal porin to Simon's HA conjugate to produce the conjugate of the instant invention, using an art known conjugation technique, with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of improving the immunogenicity of Simon's HA product by attaching a polypeptide that advantageously serves as an effective adjuvant in addition to serving as a carrier as taught by Blake *et al.* From Simons' express teaching that antigens used to couple to the low molecular weight HA are those 'that are usually employed in vaccines', one of skill in the art would readily understand that Blake's meningococcal porin polypeptide qualifies as one such antigen 'usually employed in vaccines'.

Claim 11 is *prima facie* obvious over the prior art of record.

Objection(s)

19) In line 8 of claim 1, for clarity, it is suggested that Applicants replace the limitation 'and said immunogenic conjugate' with --and wherein said immunogenic conjugate--.

Relevant Prior Art

20) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Applicants argue that the polysaccharide-benzoquinone complex reacted with BSA from Fillit's disclosure does not result in a covalent since the link between the polysaccharide and

benzoquinone is not covalent and the bond between the polysaccharide-benzoquinone complex and BSA is unstable and reversible to free components. However, the US patent issued to Francis Michon and Milan Blake *et al.* (US 5,866,135) discloses that Fillit's product comprising GASP reacted with benzoquinone and then reacted with phosphotidylethanolamine results in an immunogenic GASP-liposome covalent conjugate (see Example 1, last full paragraph in column 10; and paragraph bridging columns 1 and 2).

Remarks

21) Claims 1, 4-11, 13-18 and 29 stand rejected.

22) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

23) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

June, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER